Number of Cervical Biopsies and Sensitivity of Colposcopy

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OBJECTIVE: To examine the influence that type of medical training and number of biopsies have on sensitivity of colposcopically guided biopsies.

METHODS: Among 408 women with an adequate enrollment colposcopy and a diagnosis of cervical intraepithelial neoplasia (CIN) 3 or cancer (CIN 3+) over 2 years in the Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions (ASCUS-LSIL) Triage Study, we evaluated factors influencing the sensitivity of the enrollment colposcopic procedure. We used contingency table analysis to examine confounding variables and χ^2 tests to ascertain statistical significance.

RESULTS: Overall, 69.9% of women with a cumulative diagnosis of CIN 3+ had a "true-positive" enrollment colposcopically guided biopsy result of CIN 2 or worse (CIN 2+), the threshold that would trigger excisional therapy. The sensitivity of the procedure did not vary significantly by type of colposcopist. However, the sensitivity was significantly greater when the colposcopists took two or more biopsies instead of one ($P<.01$), a pattern observed across all types of colposcopists. Independent of the severity of the colposcopic impression, the frequency with which colposcopists took two or more biopsies instead of one varied (in descending order) from nurse practitioners to general gynecologists to gynecologic oncology fellows to gynecologic oncologists ($P<.01$).

CONCLUSION: Colposcopy with guided biopsy or biopsies detects approximately two thirds of CIN 3+. Although the sensitivity of the procedure does not differ significantly by type of medical training, it is greater when two or more biopsies are taken.

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See related editorial on page 246.

* *For a complete list of members of The Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS) Group, see the Appendix.*

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Currently, colposcopy is recommended for women with low-grade squamous intraepithelial lesion (LSIL) or worse cytology, or atypical squamous cells of undetermined significance (ASC-US) that persists or is associated with high-risk human papillomavirus (HPV) infection.[1–3] The major purpose of colposcopy in the United States is to diagnose precancerous lesions (cervical intraepithelial neoplasia [CIN] 3, especially) that can be treated to prevent cancer. However, colposcopy is a subjective procedure with limited reliability and, in particular, is not optimally sensitive for detection of CIN 3.[4–8] Reasons for the poor reproducibility of colposcopic impression and limited accuracy of colposcopically directed biopsy

have been questioned for decades.[6,9–15] One measure of the accuracy of colposcopically guided biopsy–concordance between cervical biopsy and subsequent, complete histologic diagnosis by conization, loop electrosurgical excision procedure (LEEP), or total hysterectomy–is known to be influenced by the severity of referral Pap test, patient age and menopausal status, visibility of the squamocolumnar junction, lesion size, and endocervical extension.[16–19]

Recent research has suggested that the limitations of the colposcopic examination can be reduced by taking additional biopsies. Two studies found that taking additional biopsies in quadrants where no lesion was visualized improved sensitivity of the overall colposcopic procedure (Sellors J, Qiao Y, Bao Y, Ren S, Lim J, Zhao F, et al. False-negative colposcopy: quantifying the problem. In: Book of Abstracts: 22nd International HPV Conference and Clinical Workshop 2005; 2005 April 30–May 6; Vancouver, B.C., Canada: UCSF; 2005. Poster Presentation P-490).[20] These studies were conducted in underscreened populations and are perhaps not fully applicable to the United States. Additional concern has been expressed regarding the importance of training and experience in colposcopic examinations and the possibility of differences in accuracy among various types of clinicians ranging from primary care to referral practices.[14,16,21–26]

Within the context of a large clinical trial with several thousand colposcopic examinations and 2 years of follow-up, we were able to study the influences on sensitivity of colposcopic impression and colposcopically guided biopsy relative to a reference disease standard of histologic CIN 3+. In particular we evaluated the importance of varying types of medical training: nurse practitioners, general gynecologists, gynecologic oncology fellows, and gynecologic oncologists. We also examined the extent to which confounding or mediating factors such as the number of biopsies and patient characteristics could explain any differences or similarities in accuracy among types of medical training.

MATERIALS AND METHODS

The Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions (ASCUS-LSIL) Triage Study (ALTS) was a randomized trial directed by the National Cancer Institute (National Institutes of Health, Bethesda, MD) that compared three triage strategies for women with ASCUS or LSIL. Details of the design, methods, and primary results of ALTS have been published extensively elsewhere.[1,2,27] Briefly, women with ASCUS or LSIL cytology were recruited to participate in the study at four clinical centers: University of Alabama at Birmingham (Birmingham, AL), Magee-Womens Hospital of the University of Pittsburgh Medical Center Health System (Pittsburgh, PA), the Oklahoma University Health Sciences Center (Oklahoma City, OK), and the University of Washington (Seattle, WA). The National Cancer Institute and local institutional review boards approved the study. A total of 5,060 women enrolled in the study from January 1997 to December 1998. The ALTS participants were followed up at 6-month intervals for 2 years. Routine follow-up and exit visits concluded in January 2001.

At enrollment, the ALTS participants were referred to colposcopy depending on study arm. In the immediate colposcopy arm, all women had colposcopy at, or soon after, the enrollment, regardless of enrollment test results. In the HPV triage arm, women were referred to colposcopy if the enrollment HPV test was positive (56.4%) or missing (3.9%) or if the enrollment cytology was high-grade squamous intraepithelial lesion (HSIL), although cytology added almost no referrals. In the conservative management arm, women were referred to colposcopy if enrollment cytology was interpreted as HSIL. At the semiannual follow-up visits, regardless of randomization arm, colposcopic examinations were triggered only by HSIL cytology. At the exit visit, all women were scheduled for a colposcopic examination. Throughout the trial, women with histologic CIN 2 or worse as defined by the clinical center pathologists were treated by loop electrosurgical excision procedure (LEEP) or more extensive surgery if needed. At exit, women with persistent lower-grade lesions as well were offered LEEP to maximize safety after follow-up ended.

The enrollment examination included a pelvic examination with the collection of cells for cytology and HPV DNA testing as well as high-resolution photography of the cervix for visual screening (Cervicography, National Testing Laboratories, Fenton, MO). After liquid-based ThinPrep (Cytyc Corporation, Marlborough, MA) cytology slides were prepared, 4-mL aliquots of the residual PreservCyt samples were used for HPV DNA testing by Hybrid Capture 2 (Digene Corporation, Gaithersburg, MD). As mentioned, clinical management was based on the clinical center pathologists' cytologic and histologic diagnoses. In addition, all cytology and histology slides were sent to the Pathology Quality Control Group for independent review. Pathology Quality Control Group histologic diagnoses were masked to

cytology results and used in these data analysis to avoid center-specific variation (see below).

Colposcopic examinations were performed by nurse practitioner colposcopists, general gynecologists, gynecologic oncology fellows, or gynecologic oncologists. The standard protocol included conventional visual assessment, application of 5% acetic acid, identification of the squamocolumnar junction and transformation zone, recognition of suspected CIN lesions for biopsy and overall colposcopic impression. The overall colposcopic impression was categorized as normal or benign abnormality (cervicitis/atrophy/polyp), atypical metaplasia, low grade, and high grade or cancer. Clinicians were asked to take colposcopically directed cervical biopsies from the worst of any abnormal-looking areas. They were also asked to take additional biopsies from other areas suspicious for CIN. Endocervical curettage was performed according to the clinicians' judgment, often in cases where the transformation zone or proximal extent of a cervical lesion was not adequately visualized.

Of the 5,060 women enrolled in ALTS, 2,773 had a colposcopic examination at enrollment or soon thereafter, depending on the results of the enrollment visit. We excluded from our analysis women whose enrollment colposcopic examination (n=13) or Pathology Quality Control Group diagnosis of the biopsy was unsatisfactory (n=19) or lacking (n=5). Women who had a colposcopic impression of low grade or worse but, contrary to protocol, had no Pathology Quality Control Group diagnosis of the biopsy at enrollment (n=46) were excluded. Also excluded were women attended to by a clinician with unrecorded medical training (n=7) or medical training outside the four main types considered in this study (n=8, family practitioners).

We compared accuracy of enrollment colposcopic impression and colposcopically guided biopsy results among nurse practitioners, general gynecologists, gynecologic oncology fellows, and gynecologic oncologists. Endocervical curettage results were not considered, because they detected CIN 3+ in only 1–2% of women for whom biopsies were false-negative. Due to considerable variability among the diagnostic tendencies of pathologists from different clinical centers that confounded the results, we used the standardized Pathology Quality Control Group results. For calculations of sensitivity in detection of precancer, we categorized as "biopsy-positive" any biopsy at enrollment diagnosed by Pathology Quality Control Group as CIN 2+, because less severe diagnoses would not have triggered sufficiently intensive management.

The histologic disease outcome for this analysis included CIN grade 3 and cancer (n=5) as diagnosed by Pathology Quality Control Group for a woman at any time during ALTS. We chose this definition because CIN 3 provided a scientifically rigorous endpoint for analysis.[1,2,28] Cervical intraepithelial neoplasia 3+ cases were evenly distributed by study arm over the 2-year study period, unlike less reproducible and more transient CIN 2 lesions exhibiting a wider range of HPV DNA results. Differences in CIN 3+ by study arm were shown to be differences in diagnosis time, not representing incident lesions. Rather, diagnoses during follow-up represented missed prevalent cases.[1]

We examined primarily the influence of the independent variables, number of biopsies taken and medical training, on the dependent variable, sensitivity of the colposcopically guided biopsies. We took into account possible confounding or mediating variables such as age, oral contraceptive pill (OCP) use, parity, enrollment cytology result, Hybrid Capture 2 result, colposcopic impression, study arm, and lesion size (when available) using standard contingency table analysis with χ^2 and Fisher exact test statistics and P values. For improved statistical stability we dichotomized those variables that were not already binary: aged younger than 30 years compared with aged 30 years or older, OCP current users compared with past or never users, parity less than three compared with three or more, cytology of HSIL compared with less than HSIL, colposcopic impression of high grade compared with less than high grade, biopsy number of one compared with two or more. Analyses were performed using Stata 8.0 analytic software (Stata Corp LP, College Station, TX).

RESULTS

Among the analytical group of 2,675 women with adequate enrollment colposcopically guided biopsy results, the 2-year cumulative risk for Pathology Quality Control Group histology diagnosis of CIN 3+ at any time during ALTS was 15.3% (Table 1). Thirty-five clinicians conducted the examinations with more than one third (34.9%) performed by a nurse practitioner, 14.4% by a general gynecologist, 23.9% by a gynecologic oncology fellow, and 26.8% by a gynecologic oncologist. Clinics were staffed by clinicians with different types of medical training: the Pittsburgh study site had more general gynecologists, the Seattle site had mostly nurse practitioners, the Birmingham site had more gynecologic oncologists and both Birmingham and Oklahoma City had gynecologic oncology fellows (Table 1). Because clinic population

Table 1. Characteristics of Enrollment Colposcopic Examination by Type of Medical Training

		Type of Medical Training				
	Total (N=2,675)	Nurse Practitioners	General Gynecologists	Gynecologic Oncology Fellows	Gynecologic Oncologists	*P**
Center						
Alabama	824 (30.8)	0	0	44.0	75.6	<.01
Oklahoma	506 (18.9)	0	0	56.0	20.6	
Pennsylvania	505 (18.9)	12.0	95.3	0	3.8	
Washington	840 (31.4)	88.0	4.7	0	0	
Patient characteristics at enrollment visit						
Age						
18-22 years	1,044 (39.0)	40.0	29.2	41.5	40.8	<.01
23-29 years	964 (36.0)	41.5	28.1	35.2	33.8	
30-75 years	667 (24.9)	18.4	42.7	23.3	25.4	
OCP use						
Never or not in past 2 years	1,005 (37.7)	27.5	51.8	36.5	44.6	<.01
Not current but used in past 2 years	470 (17.7)	16.5	12.5	19.3	20.5	
Current user	1,188 (44.6)	56.0	35.7	44.2	34.9	
Parity						
None	1,140 (42.7)	67.0	39.8	28.2	25.2	<.01
1-2	1,204 (45.0)	27.1	43.0	56.6	59.2	
3+	329 (12.3)	5.8	17.2	15.2	15.6	
Cytology						
Normal	745 (28.0)	19.5	26.9	32.7	35.6	<.01
ASCUS	703 (26.5)	31.7	31.1	18.8	24.0	
LSIL	792 (29.8)	28.6	29.5	32.2	29.4	
HSIL	418 (15.7)	20.2	12.5	16.4	11.1	
HC2						
Negative	581 (23.0)	20.9	35.7	18.2	23.1	<.01
Positive	1,948 (77.0)	79.1	64.3	81.8	76.9	
Characteristics of enrollment colposcopic examination						
Colposcopic impression						
Normal/cervicitis/atrophy/polyp	544 (20.3)	13.9	25.8	27.2	19.6	<.01
Atypical metaplasia	247 (9.2)	11.6	16.4	4.5	6.6	
Low grade	1,514 (56.6)	60.2	45.8	54.6	59.5	
High grade	370 (13.8)	14.4	12.0	13.6	14.4	
Number of biopsies						
0	538 (20.1)	15.6	23.4	25.7	19.2	<.01
1	1,458 (54.5)	43.3	52.3	54.0	70.8	
2	542 (20.3)	30.1	19.3	18.6	9.5	
3+	137 (5.1)	11.0	5.0	1.7	0.6	
Enrollment colposcopically directed Pathology QC biopsy result						
Normal appearance (no biopsy)	538 (20.1)	15.6	23.4	25.7	19.2	<.01
Normal biopsy	1,079 (40.3)	43.4	39.8	33.5	42.8	
Atypia	47 (1.8)	2.5	2.1	1.4	1.0	
CIN 1	531 (19.9)	20.8	18.5	21.3	18.1	
CIN 2	261 (9.8)	9.0	7.6	10.0	11.7	
CIN 3+	219 (8.2)	8.8	8.6	8.1	7.2	
2-year cumulative risk of disease (final disease outcome):						
Less than CIN 2	1,947 (72.8)	69.2	79.2	71.1	75.6	<.01
CIN 2	320 (12.0)	14.8	6.5	13.2	10.2	
CIN 3 or worse	408 (15.3)	16.1	14.3	15.8	14.2	

OCP, oral contraceptive pill; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions; HC2, Hybrid Capture 2; QC, Quality Control Group; CIN, cervical intraepithelial neoplasia.

Data are n (%) or %.

* By χ^2 test.

characteristics and types of medical training covaried by center, patient characteristics differed among types of medical training. For example, patients seeing nurse practitioners (primarily in Seattle) were more likely to be current OCP users, nulliparous and have an enrollment HSIL cytology result, whereas those examined by general gynecologists were more likely to be older and to test negative for a high-risk HPV type by Hybrid Capture 2. Patients attended by a nurse practitioner or gynecologic oncology fellow had a slightly higher 2-year cumulative risk for CIN 3+. We assured that these patient differences did not affect the main conclusions in ancillary analyses discussed below.

Nurse practitioners were most likely to suspect some type of abnormality upon colposcopic evaluation (Table 1) and therefore had a higher sensitivity of colposcopic impression of atypia or worse for detection of 2-year cumulative diagnosis of CIN 3+ (Table 2). The sensitivity of a low-grade or high-grade colposcopic impression did not differ by type of clinician training (Table 2).

The tendency to take more than one biopsy varied by clinician type from (in descending order) nurse practitioners to general gynecologists to gynecologic oncology fellows to gynecologic oncologists. The practice of taking two or more biopsies as opposed to one also varied by colposcopic impression, because clinicians were more likely to take two or more biopsies when a worse lesion was suspected (Fig. 1, far right). Both factors, type of training and colposcopic impression, contributed to an increased tendency to take two or more biopsies (Fig. 1).

The sensitivity of Pathology Quality Control Group biopsy diagnosis from the enrollment colposcopic examination to detect 2-year cumulative CIN 3+ varied depending on the number of biopsies taken (Table 3). Sensitivity is defined as the percent of enrollment colposcopically guided biopsy procedures with a histology result of CIN 2 or more that would trigger LEEP among women eventually found to have CIN 3+. Among all women with a 2-year cumulative occurrence of CIN 3+, those who had only one biopsy were less likely to be diagnosed as having CIN 2 or worse by Pathology Quality Control Group (68.3%) than those who had two (81.8%) or three or more (83.3%) biopsies (comparing one with two or more biopsies, $P<.01$).

Table 4 examines the sensitivity of a colposcopically guided biopsy by type of medical training and number of biopsies taken. Of the five patients in this ALTS analysis that had cancer, 3 had CIN 2 or worse on their enrollment colposcopically guided biopsy as determined by Pathology Quality Control Group. The calculations of overall sensitivity include 26 women who were eventually found to have CIN 3+ but had no biopsy at enrollment because their colposcopic impression was normal or benign abnormality. Overall sensitivity among clinicians from different types of medical training showed only minor variability, ranging from 67.3% for gynecologic oncology fellows to 76.4% for general gynecologists. Across all types of medical training the sensitivity of colposcopically guided biopsy tended to be greater when two or more biopsies were taken as opposed to one, although these relationships were not statistically significant. When patients for whom no biopsy was taken were included, across all levels of medical training, sensitivity was significantly greater when taking two or more compared with zero or one biopsy ($P<.03$).

Table 2. Colposcopic Impression at Enrollment Colposcopic Examination Among Patients With a 2-Year Cumulative Final Disease Outcome of Cervical Intraepithelial Neoplasia 3+, by Type of Medical Training*

	Type of medical training								
	Nurse Practitioners		General Gynecologists		Gynecologic Oncology Fellows		Gynecologic Oncologists		
Colposcopic Impression		Cumulative %		Cumulative %		Cumulative %		Cumulative %	*P**
High grade	53 (35.3)	35.3	16 (29.1)	29.1	44 (43.6)	43.6	39 (38.2)	38.2	.312
Low grade	84 (56.0)	91.3	31 (56.4)	85.5	46 (45.5)	89.1	53 (52.0)	90.2	.666
Atypical metaplasia	9 (6.0)	97.3	5 (9.1)	94.5	0 (0.0)	89.1	3 (2.9)	93.1	.064
Normal/cervicitis/atrophy/polyp	4 (2.7)	100.0	3 (5.5)	100.0	11 (10.9)	100.0	7 (6.9)	100.0	NA

NA, not applicable.
Data are n (%) or %.
* Comparison of cumulative percent by χ^2 test

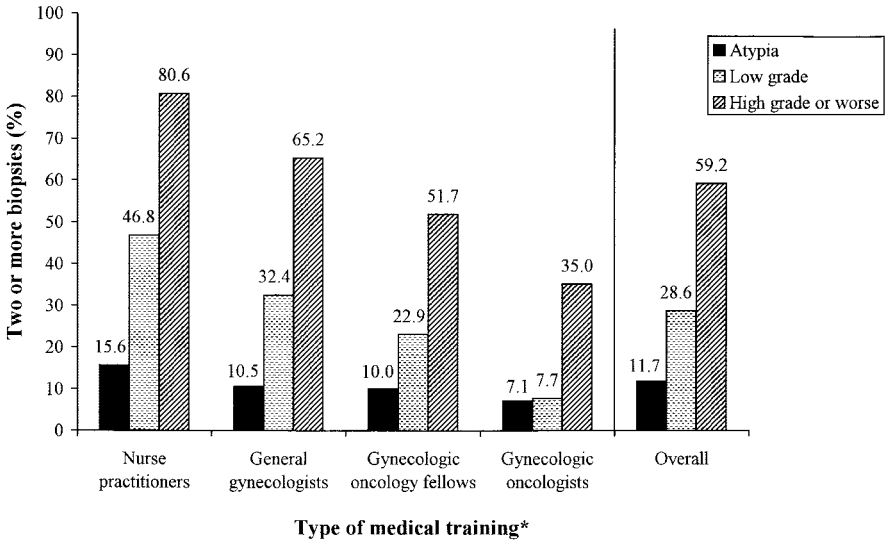

Fig. 1. Percent of colposcopic procedures with two or more biopsies taken (compared with one), given colposcopic impression of atypia, low grade or high grade or worse. Overall values and those stratified by type of medical training are separated by the vertical line. *By Fisher exact test comparing less than one with two or more biopsies across medical training: $P=.595$ for atypia impressions and $P<.01$ for both low grade and high grade impressions.

Gage. Sensitivity of Colposcopy With Guided Biopsies. Obstet Gynecol 2006.

Table 3. Enrollment Colposcopically Directed Biopsy Result Among Patients With a 2-Year Cumulative Final Disease Outcome of CIN 3+, by Number of Biopsies Taken at Enrollment Exam*

	Number of Biopsies Taken						
	One		Two		Three or More		
Enrollment Colposcopically Directed Biopsy Result*		Cumulative %		Cumulative %		Cumulative %	P†
CIN 3+	108 (51.9)	51.9	87 (65.9)	65.9	24 (57.1)	57.1	.02
CIN 2	34 (16.4)	68.3	21 (15.9)	81.8	11 (26.2)	83.3	<.01
Atypia-CIN 1	27 (13.0)	81.3	13 (9.9)	91.7	4 (9.5)	92.9	<.01
Normal/benign abnormality	39 (18.8)	100.0	11 (8.3)	100.0	3 (7.1)	100.0	NA

CIN, cervical intraepithelial neoplasia; NA, not applicable.
Data are n (%) or %.
*As read by Pathology Quality Control Group.
† By χ^2 test comparing cumulative percent of one with two or more biopsies.

Because the demographic characteristics, screening test results, and colposcopic impression were associated with both type of medical training and biopsy taking as well as sensitivity, we controlled for age, OCP use, parity, enrollment cytology result, Hybrid Capture 2 result, and colposcopic impression through stratified analyses, and our findings remained consistent. In ALTS the best descriptive measure for lesion size is the total dimension score.[28] This total dimension score was only analyzed for 246 women (60.3%) because most of the blocks from Seattle, where most nurse practitioners practiced, were not made available. We have no reason to suspect that Seattle had particularly large or small lesions. A trend toward improved sensitivity when two or more biopsies were taken was observed for all but the smallest lesions, but few numbers prevented a stable analysis.

We also looked at the effect of knowledge of cytology and HPV results at the time of colposcopy because sensitivity of the procedure varied considerably by study arm (58.8% in the immediate colposcopy arm, 79.5% in the HPV triage arm, and 80.5% in the conservative management arm, $P<.01$). In the immediate colposcopy arm, colposcopy was performed before any test results were available. In the conservative management arm, cytology results only were communicated to the clinician. In the HPV triage arm, clinicians were aware of cytology and

Table 4. Sensitivity of an Enrollment Colposcopically Directed Biopsy Result* of Cervical Intraepithelial Neoplasia 2+ to Detect a 2-Year Cumulative Final Disease Outcome of Cervical Intraepithelial Neoplasia 3+, by Number of Biopsies and Type of Medical Training

Type of Medical Training	Combined Sensitivity	Number of Biopsies: No Biopsy Taken	One	Two	Three or More	$P^{\dagger}$
Combined sensitivity	285/408 (69.9)	0/26 (0.0)	142/208 (68.3)	108/132 (81.8)	35/42 (83.3)	<.01
Nurse practitioners	105/150 (70.0)	0/7 (0.0)	34/52 (65.4)	48/61 (78.7)	23/30 (76.7)	.10
General gynecologists	42/55 (76.4)	0/4 (0.0)	18/25 (72.0)	18/20 (90.0)	6/6 (100.0)	.06
Gynecologic oncology fellows	68/101 (67.3)	0/8 (0.0)	35/52 (67.3)	30/38 (79.0)	3/3 (100.0)	.16
Gynecologic oncologists	70/102 (68.6)	0/7 (0.0)	55/79 (69.6)	12/13 (92.3)	3/3 (100.0)	.05
$P^{\ddagger}$	.640	NA	.698	.456	.114	

NA, not applicable.
Data are n/N (%).
* As read by Pathology Control Group
† By χ^2 test comparing one with two or more biopsies by type of medical training.
‡ By Fisher exact test comparing type of medical training by number of biopsies

HPV results. We found that for women with enrollment cytology findings of HSIL, clinician knowledge of the results at colposcopy led them to take more biopsies in the HPV triage and conservative management arms compared with the immediate colposcopy arm. Among HPV-positive women with a final outcome of CIN 3+, there was a suggestion of better targeting of lesions per biopsy (higher sensitivity) in the HPV arm compared with the other two arms (data not shown).

DISCUSSION

We found substantial improvement of colposcopically guided biopsy sensitivity when clinicians took more biopsies from colposcopically abnormal areas. This trend was observed across all types of medical training. While these findings suggest an important strategy to improve the accuracy of colposcopically guided biopsy with minimal effort, the appropriate location for additional biopsies remains unknown, because limited data are available to guide placement of additional biopsies. As a result of variation in the sensitivity of colposcopy, several authors have suggested taking multiple biopsies.[9,10] Some studies suggest that high-grade lesions might not always be at the point of maximal colposcopic abnormality.[20,24,29] The question of whether to take additional biopsies around the worst visualized lesion, from abnormal areas outside the worst lesion, from normal areas outside the lesion, or random biopsies of all quadrants even when no lesion is visualized, merits further research in a randomized controlled trial specifically designed to evaluate these aspects. The ALTS was not designed to examine the influence of biopsy-taking practices on sensitivity of colposcopically guided biopsy.

In addition, the best way to optimize taking of biopsies remains an issue. Colposcopy instructors can suggest ways to overcome concerns about taking multiple biopsies because instruments vary in size and sharpness. Frequent sharpening of the biopsy forceps decreases pain and tissue trauma. Proper waiting time after application of topical anesthesia and use of verbal reassurance seem to be helpful in reducing pain. Because the biopsies can be submitted in one vial, multiple sampling would not need to increase the cost of pathology. As an extreme, it would be wrong to conclude that LEEP should be used instead of biopsy because it provides the largest surface area for histology, because the procedure has been associated with uncommon, but significant, short-term and pregnancy complications.[30–33]

We have found in our clinical colposcopy instruction that most training does not specify if, or when, more than one biopsy should be taken. Although the ALTS protocol encouraged all clinicians to take additional directed biopsies of any suspected lesions, not all clinicians were equally likely to take additional biopsies. The nurse practitioners received training that encouraged additional biopsy-taking. Our data suggest that certain clinicians such as gynecologic oncologists, gynecologist fellows, and to a less degree, general gynecologists feel a greater assurance in their ability to adequately capture the worst lesions with one biopsy. In fact, gynecologic oncologists and gynecologic oncology fellows did have a relatively higher sensitivity on the first biopsy sample (data not shown), although this did not translate into higher

sensitivity of the colposcopy procedure as a whole, because general gynecologists and in particular nurse practitioners took more biopsies resulting in comparable overall sensitivities.

There is a belief that clinicians take more biopsies in the beginning of their training and take fewer later in their career as the skill of colposcopic evaluation improves. Another common assumption is that types of medical training, from nurse practitioners to general oncologists to gynecologic oncologists, form a continuum that corresponds to expertise in performing colposcopy. Our findings contradict these notions, because the overall sensitivity of the colposcopy procedure was similar across types of medical training.

This study involved colposcopic examination of women with ASCUS or LSIL cytology and may not be generalizable among women with rarer cytology results such as atypical glandular cells, HSIL or atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion. Another limitation of this study is the infrequency with which clinicians other than nurse practitioners took two or more biopsies. However, there were consistent trends of increased sensitivity when taking two or more biopsies across types of clinician training and overall, a significant increase in overall sensitivity when taking two or more biopsies. We found that sensitivity was higher among women who were younger, with lower parity, worse cytology, HPV-DNA positivity, and high-grade colposcopic impression. Within levels of each of these variables, the sensitivity of the colposcopic examination still increased with more biopsies taken (although the trends were not always statistically significant). Although we cannot absolutely rule out that differences in sensitivity were due to unmeasured differences in clinic populations such as lesion size, visibility of squamocolumnar junction, or endocervical extension, the patterns were consistent across levels of measured, possible confounding variables.

These results show that across various types of medical training, colposcopic impressions and colposcopically guided biopsies demonstrate similar sensitivities. Colposcopy, like cytology and histology, is subjective, and the number of colposcopically guided biopsies taken is most strongly associated with sensitivity. As women are referred to colposcopy based on increasingly sensitive screening tests, there is a need to have a diagnostic examination with the best accuracy possible.

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APPENDIX

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